REMARKS

Claims 1-22 are pending. Claims 3, 5, 6 and 11-22 have been cancelled as being directed to a non-elected invention. Following entry of the amendments, claims 1, 2, 4 and 7-10 will be under examination. Applicants have reviewed the rejections set forth in the Office Action mailed June 15, 2005, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4 and 7-10 stand rejected under 35 U.S.C. § 103 (a) as obvious over Edwards et al. (2000) in view of Varner et al. and Berry. The Office alleges that Edwards et al. describes a method of determining optimal growth in *E. coli* using a computational metabolic flux balance analysis which may be used to design metabolic networks in cells for industrial and research purposes. The Office concedes that Edwards et al. does not describe culturing engineered cells to allow expression of an optimal function or the introduction or alteration of genes. Varner et al. is alleged to describe computer-implemented models to predict growth or metabolism of genetically altered and cultured cells. Berry is alleged to describe an *in vitro* method, including flux analysis, for optimizing production of products by culturing genetically engineered cells under conditions which allow the cells to evolve to a desired or enhanced level of production. The Office concludes that it would have been obvious to design cells by the methods of Edwards et al. and culture them as described by Berry because one would have been motivated to grow cells designed for optimal production of a product as taught by Berry and suggested by Edwards' description to design cells for industrial use. The description by Edwards et al. and Varner et al. that optimal reaction networks is desirable is asserted to provide further motivation to design and culture cells as alleged above. Those skilled in the art would have expected culturing cells designed *in silico* using the method of Berry to succeed allegedly because Berry describes that his method of engineering relates to flux analysis.

The claimed invention is directed to a method for achieving an optimal function of a biochemical reaction network in a cell. The method includes calculating optimal properties of a

biochemical reaction network, altering reactions, re-computing optimal properties until a desired optimal function is reached and cultivating a genetic makeup of a cell having the resultant reaction network under conditions to allow the cells to evolve to the desired optimal function determined by the re-computations. The combination of Edwards et al., Varner et al. and Berry fail to teach or suggest the invention as claimed. Similarly, neither Edwards et al., Varner et al. or Barry provide any motivation to construct a genetic makeup of a cell containing biochemical reactions specifying optimal properties and evolving the cell to the desired optimal function under a specified condition.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, at least because all elements of the claimed method for achieving an optimal function of a biochemical reaction network are not taught or suggested by the cited art. The pending claims recite altering a list of reactions in a biochemical reaction network and re-computing the optimal properties until a desired optimal function is reached. Cells constructed to contain the biochemical reactions which result in the desired optimal function are cultivated to evolve to the desired optimal function of the re-computed biochemical reaction network. The combination of Edwards et al., Varner et al. and Barry fail to teach or suggest re-computing optimal properties of an *in silico* biochemical reaction network until a desired optimal function is reached and cultivating a genetic makeup of a cell having the resultant reaction network to evolve to the previously determined optimal function when it the reaction network is replicated in a cell.

For example, Edwards et al. appears to describe the assembly of strain-specific data to define an *in silico* representation of a metabolic network for a selected group of single cellular organisms. Varner et al. appears to describe mathematical models of metabolic pathways. Neither Edwards et al. or Varner et al. appear to teach or suggest culturing of cells. The description cited in the Office Action at page 933 of Edwards et al. purports to corroborate

certain legacy data, but without comparison between the *in silico* and the cell culture characteristics for an optimal function. Barry similarly fails to describe culturing a genetic makeup of a cell containing biochemical reactions resulting in a desired optimal function to evolve to that desired optimal function. Rather, Barry appears to describe that cells produce product at higher yields when cultured in a fed-batch fermentation process (Figure 2) or when a biosynthetic pathway is manipulated to alter the availability of carbon precursors. Because Barry describes a fermentation process or manipulation of a biosynthetic pathway, Barry does not teach or suggest the claimed element to constructing a genetic makeup of a cell containing a biochemical reaction network specifying optimal properties and evolving the cell to the desired optimal function under a specified condition. In the absence of such a teaching or suggestion for each element of the claimed method, the Office has not established a *prima facie* case of obviousness of any of the claims under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Further, where an invention is contended to be obvious based upon a combination of elements across different references, the Federal Circuit case law "require that there be a suggestion, motivation or teaching to those skilled in the art for such a combination." *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." *Id.* (citing *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1371-72 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (abrogated on other grounds)).

Applicants respectfully submit that the cited combination of references fails to teach, suggest or motivate those skilled in the art to combine elements of the method of the invention as they are claimed. For example, the cited references fail to provide a teaching, suggestion or motivation for the claimed combination because Edwards et al. and Varner et al. focus on whether their *in silico* modeling methods can be used to predict behavior or are sufficiently

reliable for the construction of other *in silico* models and Barry describes processes unrelated to evolution in culture.

In this regard, Edwards et al. describes that any culturing of cells predicted by the described model is for "experimental verification" for the "further development of *in silico* strains and their use to represent their *in vivo* counterparts." Edwards et al., page 938, col. 2, para. 3 (emphasis added). Thus, Edwards et al. is focused on the design of *in silico* models that may be useful as an authentic replica of an *in vivo* cell rather than culturing a genetic makeup to evolve to a desired optimal function. Varner et al. similarly is focused on the ability of mathematical models to accurately predict metabolic pathways and is completely silent as to any actual construction of a genetic markup of an *in silico* model. Barry describes fed-batch fermentation and biosynthetic pathway manipulation unrelated to evolution in culture and concludes that implementation of a genetic alteration redirecting carbon availability may be promising (see, for example, paragraph bridging pages 251-52; page 252, col. 2, para. 2; page 254, col. 2, last paragraph, and page 255, col. 2, para. 1). Further, Berry's use of the term "flux analysis" refers to the technique of experimentally determining the flux distribution of metabolism. This use is distinct from the Applicants use of "flux balance analysis" in the claimed invention because flux balance analysis refers to the technique of calculating an optimal flux distributions computationally. Neither culturing for experimental verification as described by Edwards et al. or experimentally determining metabolic fluxes as described by Barry teach, suggest or provide a motivation for the claimed requirement for culturing to evolve to an optimal function.

The above descriptions in the cited art appear consistent with how computational models were used prior to Applicants' invention or how experimental fluxes were determined generally. However, none of these descriptions teach, suggest or provide a motivation for requiring culturing to evolve to an optimal function that is specified genetically because there is no description or suggestion relating to an adaptive culturing period that allows an evolution to occur. Prior to Applicants' invention, a computational model was generally used as a prediction

for how a cell should perform given a set of conditions. The results of a prediction or a computationally-derived hypothesis was compared to experimental data to determine accuracy of performance. If the model was inconsistent with the experimental data the conclusion generally was that the model was wrong. Rarely did one conclude that the model was right and that the cell was not optimal. Similarly, it also was rare to conclude that one could make the cell optimal as specified by the model because when an inconsistency arose between a model and experimental results, the conclusion was that the model was incorrect. The present invention is directed to this discovery because it claims culturing a genetic makeup to evolve to an optimal function that is specified by the computational model. Absent a teaching, suggestion or motivation that evolution in culture is required to achieve a desired optimal function, although the genetic makeup contains a biochemical reaction network specifying optimal properties, the cited references cannot render the claimed invention obvious.

Further, if the Office were to maintain the instant rejection, obviousness can be rebutted where it is shown that the prior art taught away from the claimed invention. *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 7 (Fed. Cir. December 14, 2004) (citing *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997)).

As set forth in Applicants' previous response and further below, the cited references teach away from the claimed method of producing a genetic makeup of a cell containing a biochemical reaction network having optimal properties and culturing that genetic makeup to evolve it to a desired optimal function specified by the network. For example, Edwards et al. teaches away from culturing a genetic makeup of a cell to evolve to a desired optimal function specified by a biochemical reaction network having optimal properties when Edwards et al. states:

> The analysis of the metabolic phenotype-genotype relation using the bioinformaticaly based *in silico* metabolic genotype of *E. coli* can serve as a basis for the construction of parallel *in silico* representations of other single-cell organisms. . . . Utilizing the techniques described herein, information can be

> gained regarding the metabolic physiology of a cell with relatively little experimental biochemical information on the cell of interest.

Edwards et al. at page 938, col. 2, para. 3 (emphasis added).

Any assertion that obviousness has been established is precluded by this teaching away in the primary reference for a culturing step to evolve to a desired optimal function because Edwards et al. teaches that physiological information can be obtained from the model with little experimental information. Further, both Edwards et al. and Varner et al. conclude that their models are sufficiently reliable to form the basis of other *in silico* models. Therefore, the references also cannot suggest or provide any motivation for an evolutionary step because they teach that such a step is unnecessary since their methods are satisfactory for the described purposes.

Accordingly, Edwards et al., Varner et al. and Berry to provide any teaching, suggestion or motivation to evolve a genetic makeup of a cell containing a biochemical reaction network specifying optimal properties to the desired optimal function as claimed by the invention. Withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Enclosed is Check No. 579528 in the amount of $60.00 for the one (1) month extension of time fee. The Commissioner is hereby authorized to charge for any additional required fees, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

Date: October 14, 2005

Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213